GUIDANCE[1,2]

CLOZAPINE TABLETS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. INTRODUCTION

A. Clinical Usage/Pharmacology

Clozapine, a dibenzodiazepine derivative, with potent antipsychotic properties, is an atypical neuroleptic drug, because, unlike other neuroleptics, it does not appear to produce significant extrapyramidal side effects (1, 2). Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment (3). Clozapine has been reported to be effective in a substantial portion (30-50%) of schizophrenic patients who are refractory to or intolerant of classic antipsychotic therapy. Despite its promising therapeutic potential, the relatively high incidence of clozapine-induced agranulocytosis (1 to 2% of patients) is a major factor restricting wide use of the drug in psychiatric practice (4). Although the exact pharmacological mechanism of action of clozapine is not fully understood, the drug does possess significant binding affinity for different dopamine receptors, with recent evidence supporting binding to the D_4 receptor sub-type (5). The

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[1] Although this guidance document, prepared by the Office of Generic Drugs, does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration or the public, it does represent the agency's current thinking on clozapine bioequivalence studies. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-594-2290; Fax: 301-594-0181).

[2] The Office of Generic Drugs has received reports of cardiovascular adverse reactions in subjects participating in clozapine bioequivalence studies. A medical consultant to the office is available to provide information about ways to prevent and, if they occur, manage these adverse reactions. Prior to initiating a clozapine bioequivalence study, sponsors are encouraged to contact the Division of Bioequivalence, Office of Generic Drugs, at 301-594-0350, to obtain assistance in contacting this consultant.

drug also acts as an antagonist at adrenergic, cholinergic, histaminergic, and serotonergic receptors. Currently, clozapine is marketed by Sandoz Pharmaceuticals Corporation under the name Clozaril®, 25 mg (scored) and 100 mg tablets. The drug may be administered without regard to meals. In order to minimize the risk of agranulocytosis, Clozaril® (clozapine) is available only through a distribution system that ensures weekly WBC testing prior to delivery of the next week's supply of medication. For initial treatment with Clozaril® (clozapine), it is recommended that treatment begin with one-half of a 25 mg tablet (12.5 mg) once or twice daily and then be continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-400 mg/day by the end of 2 weeks. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to 600-900 mg/day range to obtain an acceptable response.

B. Chemistry

Clozapine [8-Clair-11-(4-methyl-1-piperazinyl)-5H-dibenzo [1,4] diazepine] is a tricyclic dibenzodiazepine derivative. The structural formula is:

Clozapine occurs as a yellow, crystalline powder and is very slightly soluble in water. Commercially available clozapine tablets should be stored in tight containers at a temperature not exceeding 30 ^{o}C.

C. Pharmacokinetics

Clozapine is rapidly and almost completely absorbed following oral administration. However, because of extensive hepatic first-pass metabolism, only about 27-50% of an orally administered dose reaches systemic circulation unchanged. Gastrointestinal absorption appears to occur principally in small intestine and is

approximately 90-95% complete within 3.5 hours after an oral dose. Food does not appear to affect the systemic bioavailability of clozapine. The relative oral bioavailability of commercially available 25 mg and 100 mg clozapine tablets reportedly is equivalent relative to a clozapine solution. Following oral administration of a single 25 mg or 100 mg oral dose of clozapine as tablets in healthy adults, the drug is detectable in plasma within 25 minutes, and peak plasma clozapine concentrations occur at about 1.5 hours. Peak plasma concentrations may be delayed with higher single doses and with multiple dosing of the drug (6).

The decline of plasma clozapine concentrations in humans is biphasic. The elimination half-life of clozapine following a single 75 mg or 100 mg oral dose reportedly averages 8 hours (range: 4-12 hours). The elimination half-life of clozapine at steady state following administration of 100 mg twice daily reportedly averages 12 hours (range: 4-66 hours). Steady-state plasma concentrations of clozapine are achieved after 7-10 days of continuous dosing (6). In a multiple-dose study, a dose of 100 mg twice daily, produced an average steady state peak plasma concentration of 319 ng/mL (range: 102 - 771 ng/mL), at about 2.5 hours (range: 1-6 hours). The average minimum concentration at steady state administered the same dose was 122 ng/mL (range: 41-343 ng/mL).

Considerable interindividual variations in plasma clozapine concentrations have been observed in patients receiving the drug, and some patients may exhibit either extremely high or extremely low plasma concentrations with a given dose. Such variability may occur at high dosages (e.g., 400 mg daily) of the drug. There is some evidence that interindividual differences in pharmacokinetic parameters for clozapine may result, at least in part, from nonlinear, dose-dependent pharmacokinetics of the drug. However, a linear dose - concentration relationship also has been reported (6). Results of a study in patients with chronic schizophrenia revealed a correlation between oral clozapine doses of 100-800 mg daily and steady-state plasma concentrations of the drug. In addition, linearly dose-proportional changes in area under the plasma concentration-time curve (AUC) and in peak and trough plasma concentrations have been observed with oral dosage of 37.5, 75, and 150 mg twice daily in other studies (7).

Clozapine is approximately 95% bound to serum proteins. Clozapine is almost completely metabolized prior to excretion and only trace amounts of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The desmethylated, hydroxylated, and N-oxide derivatives are the metabolized products seen in urine and feces. The desmethyl metabolite has only limited pharmacological activity, while the hydroxylated and N-oxide derivatives are inactive.

II. *IN VIVO* BIOEQUIVALENCE STUDIES[3]

A. Product Information

1. FDA Designated Reference Product: Clozaril® 25 mg and 100 mg tablets manufactured by Sandoz Pharmaceuticals Corporation. Clozaril® 25 mg is available as scored tablet.

2. Batch size: The test batch or lot should be manufactured under production conditions and should be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 units, <u>whichever is larger</u> .

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5%.

B. Types of Study (a Fasting Single Dose or Multiple Dose Bioequivalence Study)

Clinical studies in healthy subjects and patients have revealed that clozapine-treated individuals at times experience orthostatic hypotension and severe bradycardia. In one study of 17 clozapine naive normal volunteers administered 25 mg. of clozapine, 10 subjects experienced orthostatic hypotension and 8 experienced bradycardia below 40 beats per minute (2 of these 8

[3] The sponsoring firm is advised that an Investigational New Drug Application (IND) filing may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1) and also Office of Generic Drugs Policy and Procedure Guide #36-92, Submission of an "Investigational New Drug Application" to the Office of Generic Drugs, issued October 13, 1992.